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A facile one-pot ultrasound assisted for an efficient synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitriles

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ABSTRACT

A convenient one-pot protocol was developed for the synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitrile derivatives. This reaction was carried out through a three component condensation reaction of isatins, malononitrile, and anilinolactones in the presence of a catalytic amount of Et_3N as an inexpensive and available basic catalyst in THF under ultrasound irradiation. The products were obtained in high yields and short reaction times. The main advantage of this synthetic method is that the obtained products in ultrasonic irradiations are different from classical heating.

1. Introduction

Multicomponent reactions (MCRs), in which multiple starting materials react together *via* a one-pot procedure to form a final product without isolating the intermediates, are special types of synthetically important organic reactions in combinatorial and medicinal chemistry [1–3]. Such reactions present remarkable advantages for the efficient construction of highly complex molecules in a single procedural step such as; operational simplicity, reduction in reaction steps and the number of workup, reduction in energy consumption, and high degree of atom economy [4,5]. In the past decade there have been tremendous development in three- and four component reactions and great efforts continue to be made to develop new MCRs [6].

Recently, the application of ultrasound as a powerful technique in synthetic organic chemistry became extremely efficient and attractive. The prominent features of the ultrasound approach are enhanced organic reaction rates, formation of purer products in high yields, mild reaction conditions, and considered a processing aid in terms of energy conservation and waste minimization compared with traditional methods [7,8]. Ultrasonic irradiation is widely used today in organic synthesis and has an intense impact on the way chemists approach organic and parallel synthesis, and a large number of organic reactions have been done by using ultrasonic irradiation [9–11].

Isatin (1*H*-indole-2,3-dione) and its derivatives exhibit various biological activities such as anticancer [12], anticonvulsant [13], anti-inflammatory [14], antimicrobial, antiviral [15] and antineoplastic activities [16]. These compounds are versatile building blocks for the synthesis of a large variety of heterocyclic compounds such as indoles, isatoic anhydride, quinolines, spirooxindoles, and etc. Spirooxindoles have a special place in heterocyclic chemistry due to their highly pronounced pharmacological and biological activities [17–21] as well as presence in a number of natural products, such as: *Horsfiline*, *Spirotryprostatin A* and *B*, *Elacomine*, *Pteropodine* (Fig. 1) [22–24]. The unique structural array of these compounds has made them attractive synthetic targets in chemistry [25].

As part of our current studies on the development of new efficient strategies for the preparation of spirooxindoles [26–28], in this research, we report a highly efficient one-pot, three component condensation reaction for the synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline 3-carbonitrile derivatives **4** in the presence of catalytic amount of Et_3N as an inexpensive and available catalyst in THF under ultrasound irradiation in high yields.

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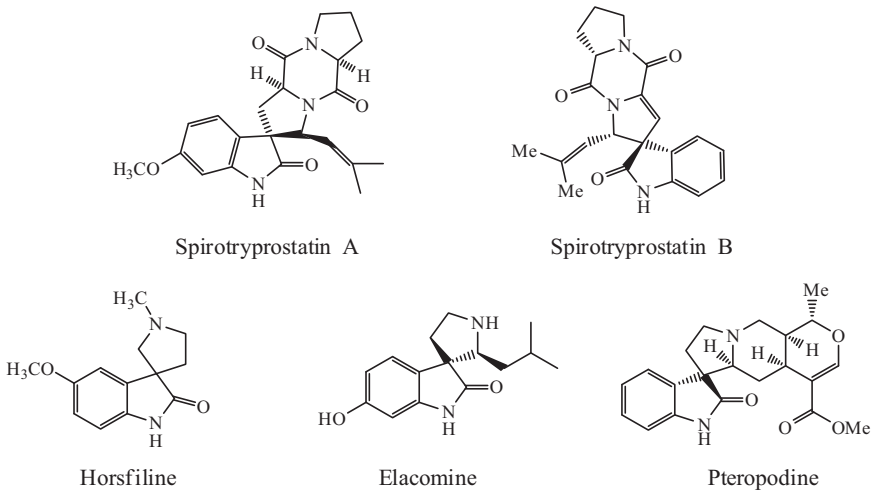

Fig. 1. Selected spirooxindolic natural products.

2. Experimental section

2.1. Materials

The chemicals used in this work were obtained from Fluka and Merck Chemical Company and were used without purification.

2.2. Apparatus

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a shimadzu QP 1100 Ex mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Ultrasound assisted reactions were carried out using a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and a nominal power of 350 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) at 50 °C. The reaction flask was located in the maximum energy area in the cleaner; where the surface of reactants (reaction vessel) is slightly lower than the level of the water. The temperature of the water bath was controlled by the addition or removal of circulated water. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.3. Typical procedure for the preparation of 2-amino-2′,5-dioxo-1-p-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4b)

A mixture of isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** (1 mmol), and Et_3N (15 mol%) in THF (5 mL) was sonicated at 50 °C. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and the precipitate washed with EtOH (2 × 5 ml) to afford the pure product **4b** as white powder (0.337 g, 88%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 2185, 1721, 1682. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.37 (3H, s, CH_3), 4.47–4.64 (2H, m, OCH_2) 5.99 (2H, s, NH_2), 6.82–7.44 (8H, m, ArH), 10.48 (1*H*, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 21.2, 48.2, 60.0, 66.1, 99.0, 109.8, 119.5, 122.5, 125.3, 128.9, 129.3, 131.2, 131.7, 134.3, 140.3, 141.8, 152.8, 159.6, 170.1, 178.0. Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58%; Found C, 68.69; H, 4.24; N, 14.53%. MS: *m/z* 384.

2.3.1. 2-Amino-2′,5-dioxo-1-phenyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′ indoline]-3-carbonitrile (4a)

White powder (0.266 g, 72%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3385, 2180, 1750, 1683. ^{1}H NMR (DMSO-d_6, 400 MHz): δppm: 4.34–4.65 (2H, m, OCH_2) 6.03 (2H, s, NH_2), 6.81–7.56 (9H, m, ArH), 10.49 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta_{ppm:}$ 48.2, 60.2, 66.1, 99.2, 109.9, 119.5, 122.5, 125.3, 129.3, 130.7, 134.3, 134.4, 141.8, 152.7, 159.5, 170.0, 178.0. Anal. Calcd for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13%; Found C, 68.16; H, 3.87; N, 15.08%; MS: *m/z* 370.

2.3.2. 2-Amino-1-(4-chlorophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4c)

Cream powder (0.298 g, 74%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3334, 2185, 1722, 1683. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.52–4.71 (2H, m, OCH_2) 6.21 (2H, s, NH_2), 6.81–7.63 (8H, m, ArH), 10.50 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.2, 60.5, 66.8, 99.3, 109.8, 115.6, 122.5, 125.4, 129.3, 130.7, 131.3, 133.4, 134.3, 135.3, 141.8, 152.7, 159.4, 170.0, 178.0. Anal. Calcd for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N%, 13.84; Found C, 62.36; H, 3.30; N, 13.79%. MS: *m/z* 406, 404.

2.3.3. 2-Amino-1-(3-chlorophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4d)

Gray powder (0.306 g, 76%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3454, 2186, 1720, 1686. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.51–4.73 (2H, m, OCH_2) 6.24 (2H, s, NH_2), 6.81–7.82 (8H, m, ArH), 10.51 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.2, 60.2, 66.1, 99.4, 109.8, 119.4, 122.5, 125.4, 128.2, 129.3, 129.7, 130.8, 132.1, 134.2, 134.6, 135.8, 141.8, 152.6, 159.2, 170.0, 177.9. Anal. Calcd for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N, 13.84%; Found C, 62.36; H, 3.19; N, 13.78%. MS: *m/z* 406, 404.

2.3.4. 2-Amino-2′,5-dioxo-1-p-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4e)

White powder (0.291 g, 76%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3448, 2187, 1713, 1680. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.30 (3H, s, CH_3), 4.33–4.70 (2H, m, CH_2O) 6.06 (2H, s, NH_2), 6.83–7.46 (8H, m, ArH), 10.52 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz):